National Institute of Neurological Disorders and Stroke

The Opioid Epidemic: How, Where, and What Can Be Done?

NIH Demystifying Medicine Lecture Series

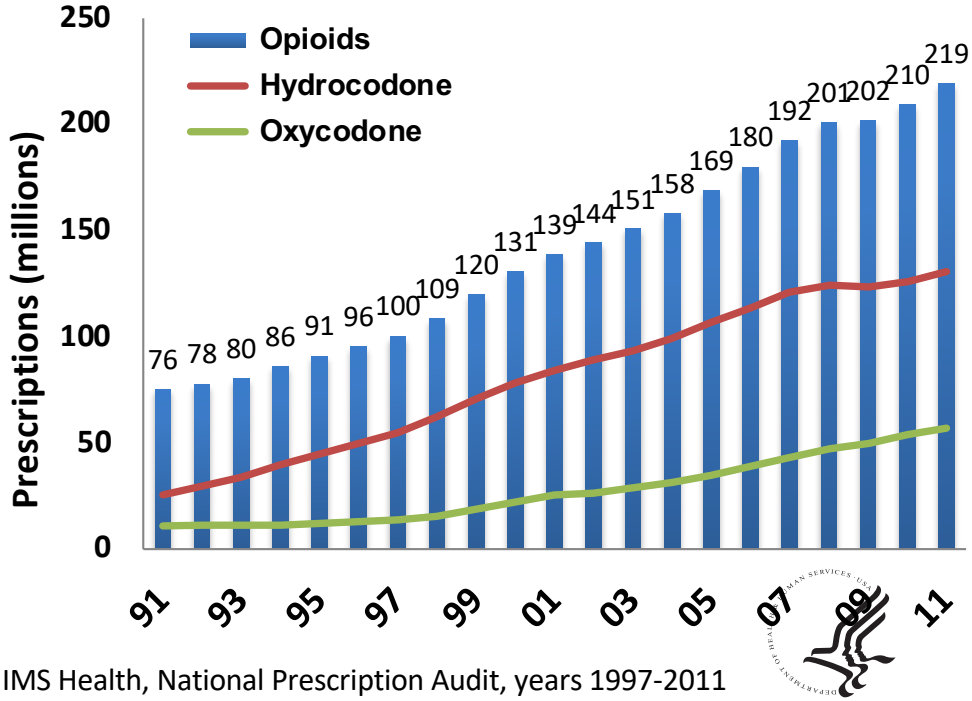
April 17, 2018

Walter J. Koroshetz, MD, FAAN

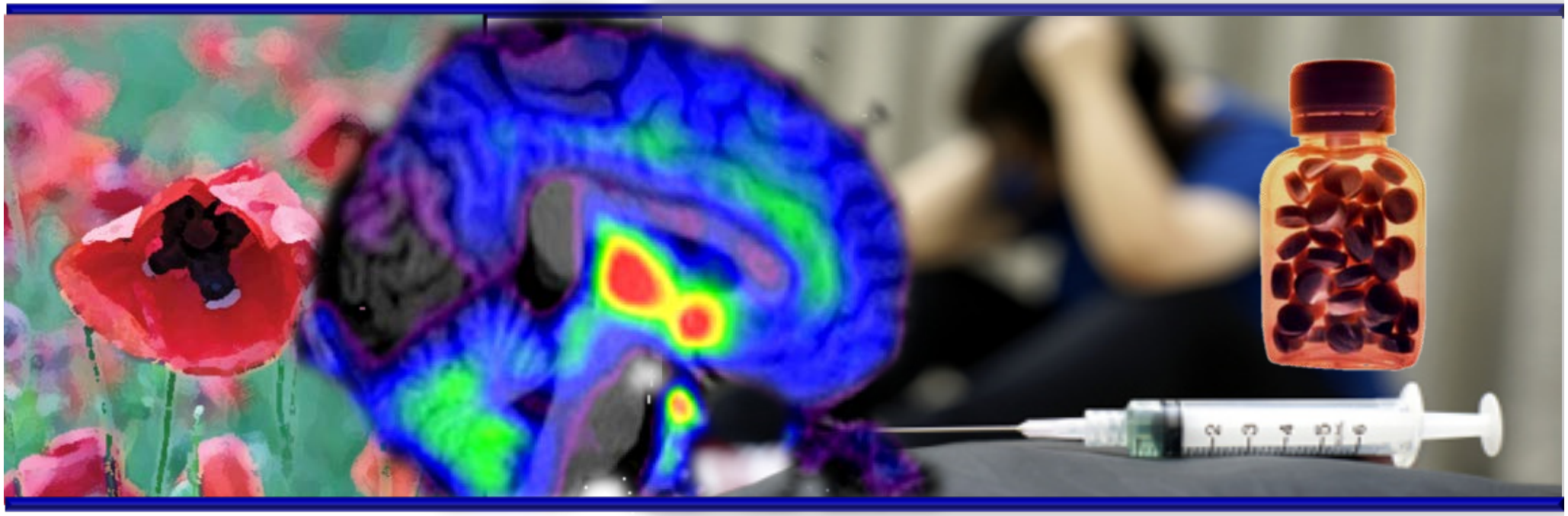
Director, National Institute of Neurological Disorders and Stroke, NIH

Balancing act of treating pain

- 100 million American adults have pain
  - 40 million have severe pain
  - 25 million report daily pain
  - 8 million have pain that interferes with lifestyle



Source: NIDA, IMS Health, National Prescription Audit, years 1997-2011



Pain is at the root of the opioid epidemic

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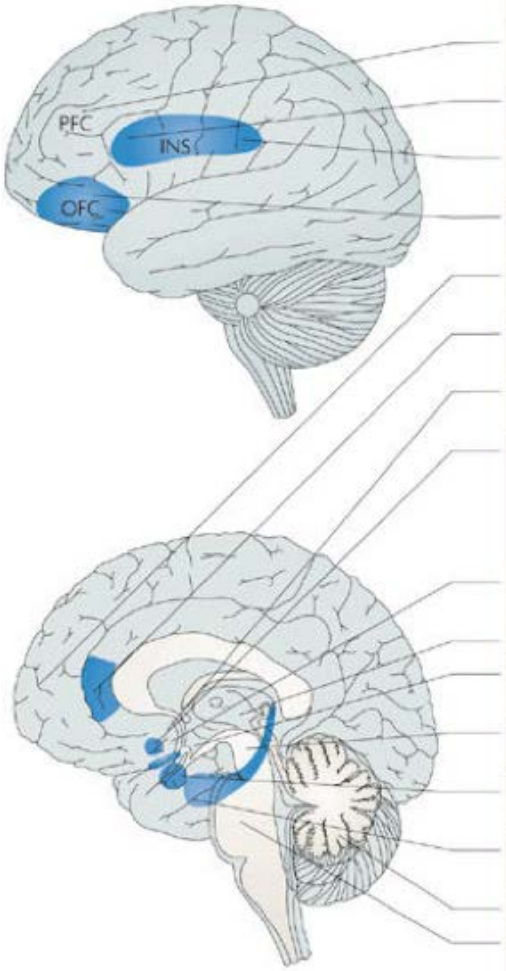
“Nature has placed mankind under the governance of two sovereign masters, Pain and Pleasure” - Jeremy Bentham

Brain regions implicated in pain and reward processing by neuroimaging and electrophysiology studies who striking overlap.



Region	Pleasure/reward	Pain
Lateral prefrontal cortex	• Humans, fMRI, taste reward[101]	• Humans, H_2O PET, hyperalgesic pain[102] • Humans, fMRI, pain[103]
Anterior insula	• Humans, fMRI, food cravings[104] • Humans, H_2O PET, chocolate reward[75]	• Humans, fMRI, pain[105] • Humans, fMRI, placebo analgesia[106]
Posterior insula	• Humans, fMRI, hypothetical reward[107]	• Humans, direct brain stimulation[108] • Humans, fMRI, pain[105]
Orbitofrontal cortex	• Humans, fMRI, pleasant touch[74] • Humans, fMRI, chocolate reward[75]	• Humans, fMRI, pain[74] • Humans, fMRI, placebo analgesia[106]
Medial prefrontal cortex	• Humans, H_2O PET, pleasurable music[64] • Humans, fMRI, monetary reward[109]	• Humans, fMRI, pain[110,111]
Anterior cingulate gyrus	• Monkeys, electrophysiology[112] • Humans, H_2O PET, chocolate reward[75]	• Humans, fMRI, pain[113] • Humans, opioid PET[43]
Dorsal striatum	• Humans, fMRI, fruit juice[114] • Humans, fMRI, monetary reward[115]	• Humans, dopamine ligand PET, pain[43] • Humans, fMRI, pain[116]
Nucleus accumbens/ ventral striatum	• Humans, fMRI and dopamine ligand PET[1], monetary reward[65] • Rodents, hedonic hotspot, taste reactivity • Humans, dopamine ligand PET[43], drug reward	• Humans, dopamine ligand PET[43] • Humans, fMRI, expectation of pain[44] • Rodents, pain-induced analgesia[20]
Ventral pallidum	• Rodents, taste reactivity[62,65]	• Rodents, tracing, pain affect[72] • Humans, μ-opioid PET, sustained pain[2]
Thalamus	• Humans, H_2O PET, chocolate reward[75]	• Humans, fMRI, placebo analgesia[106]
Hypothalamus	• Humans, H_2O PET, pleasurable music[117]	• Rodents, tracing of nociceptive pathway[72] • Humans, direct brain stimulation[118]
Midbrain	• Humans, H_2O PET, chocolate reward[75] • Humans, H_2O PET, pleasurable music[64]	• Humans, fMRI, anticipation of pain[119] • Humans, fMRI, pain[120]
Amygdala	• Humans, H_2O PET, pleasurable music[64] • Primates, reward anticipation/learning[63]	• Humans, fMRI, pain[70,120]
Hippocampus	• Humans, fMRI, unexpected reward[121] • Humans, H_2O PET, pleasurable music[64]	• Humans, fMRI, pain[122] • Humans, fMRI, anticipation of pain[119]
Cerebellum	• Humans, fMRI, unexpected reward[121]	• Humans, fMRI, pain[123]
Brainstem	• Rodents, taste reactivity[124] • Rodents, conditioned place preference[40]	• Humans, fMRI, pain[123] • Rodents, pain[40]

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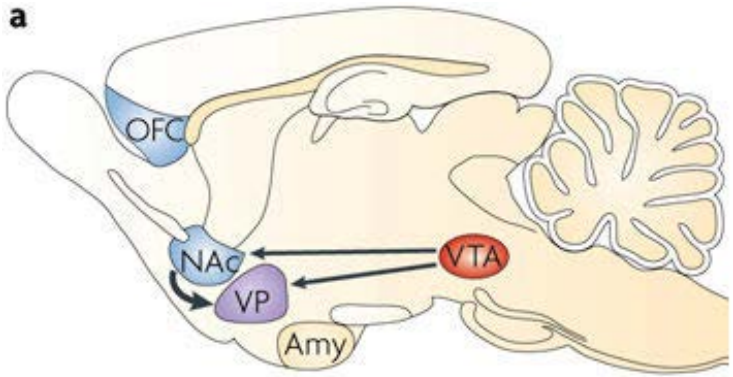
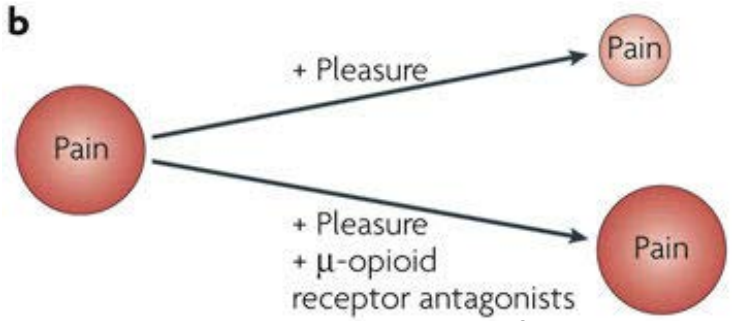
Nature Reviews | Neuroscience

Nat Rev Neurosci. 2008 Apr;9(4):314-20

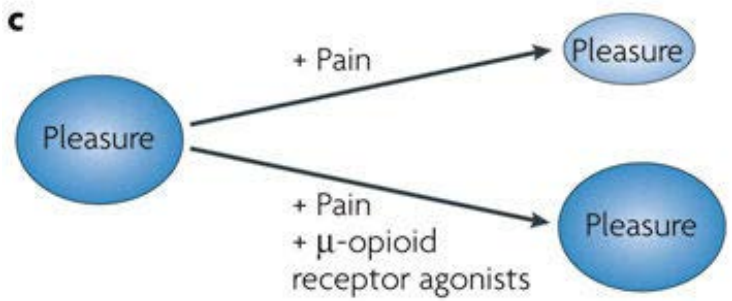
Pain v. reward

Shared pathway





Eg. naloxone



Eg. morphine

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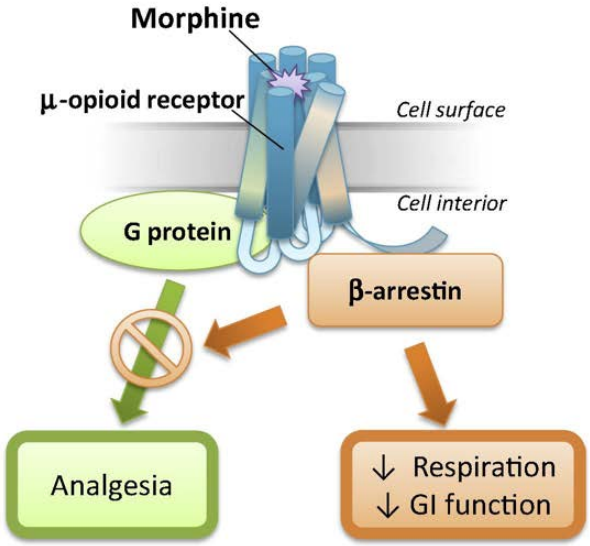
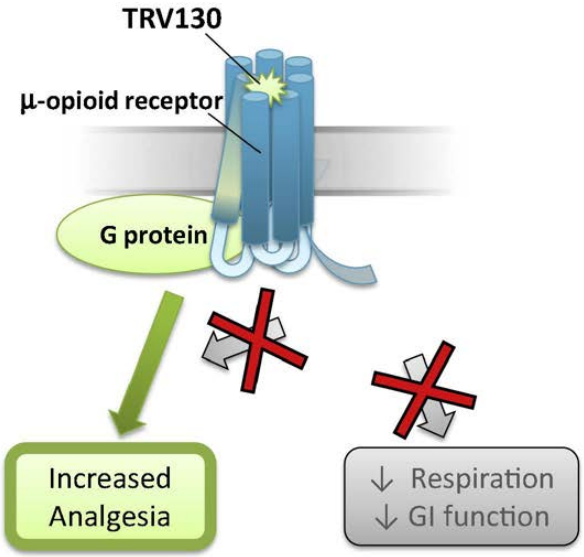
Nat Rev Neurosci. 2008 Apr;9(4):314-20

Opioid receptor mediates reward and analgesia and….death





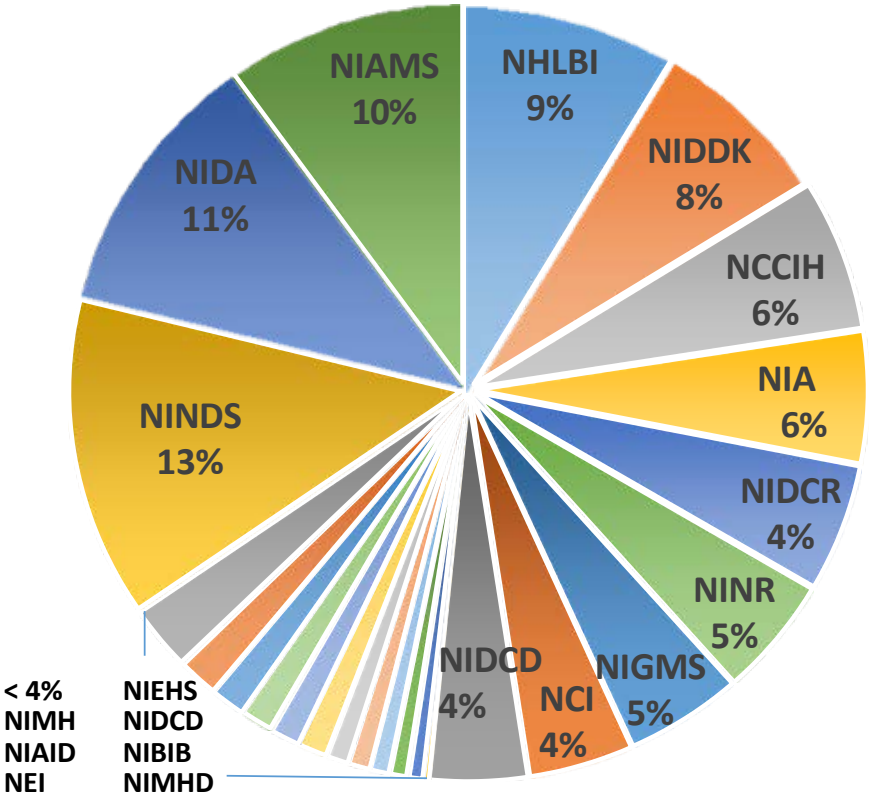
Pain. 2014 Sep;155(9):1829-35.

NIH Investment in Pain Research

In 2016, NIH invested $483 million on pain research

Pain cuts across all 27 of the NIH Institutes and Centers.

Pain Research Funding by Institutes and Centers



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The NIH Pain Consortium Membership

Mission

To enhance pain research and promote collaboration among researchers across the NIH Institutes and Centers that have programs and activities addressing pain

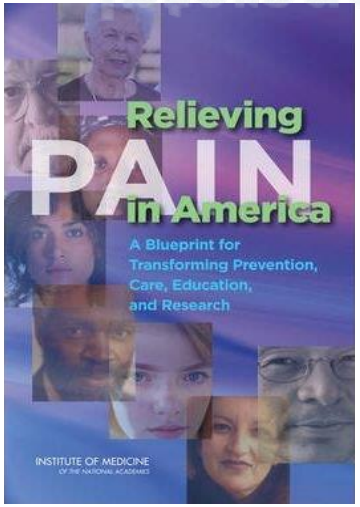
http://painconsortium.nih.gov/

National Cancer Institute
National Eye Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Disorders
National Institute on Drug Abuse
National Institute of General Medical Sciences
National Institute of Mental Health

National Institute of Minority Health and Disparities
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research
National Heart Lung and Blood Institute
National Center for Advancing Translational Science
National Center for Complementary & Integrative Health
John E. Fogarty International Center
Warren Grant Magnuson Clinical Center
Office of Science Policy and Analysis
Office of Behavioral and Social Sciences Research
Office of Technology Transfer
Office of Research on Women's Health
Office of Rare Diseases

Institute of Medicine report led to the National Pain Strategy

The Interagency Pain Research Coordinating Committee



In response to the IOM's core recommendations:
"The NPS is the government's first broad-ranging effort to improve how pain is perceived, assessed, and treated: a significant step toward the ideal state of pain care."

Coordinated roadmap toward improving U.S. pain care in:

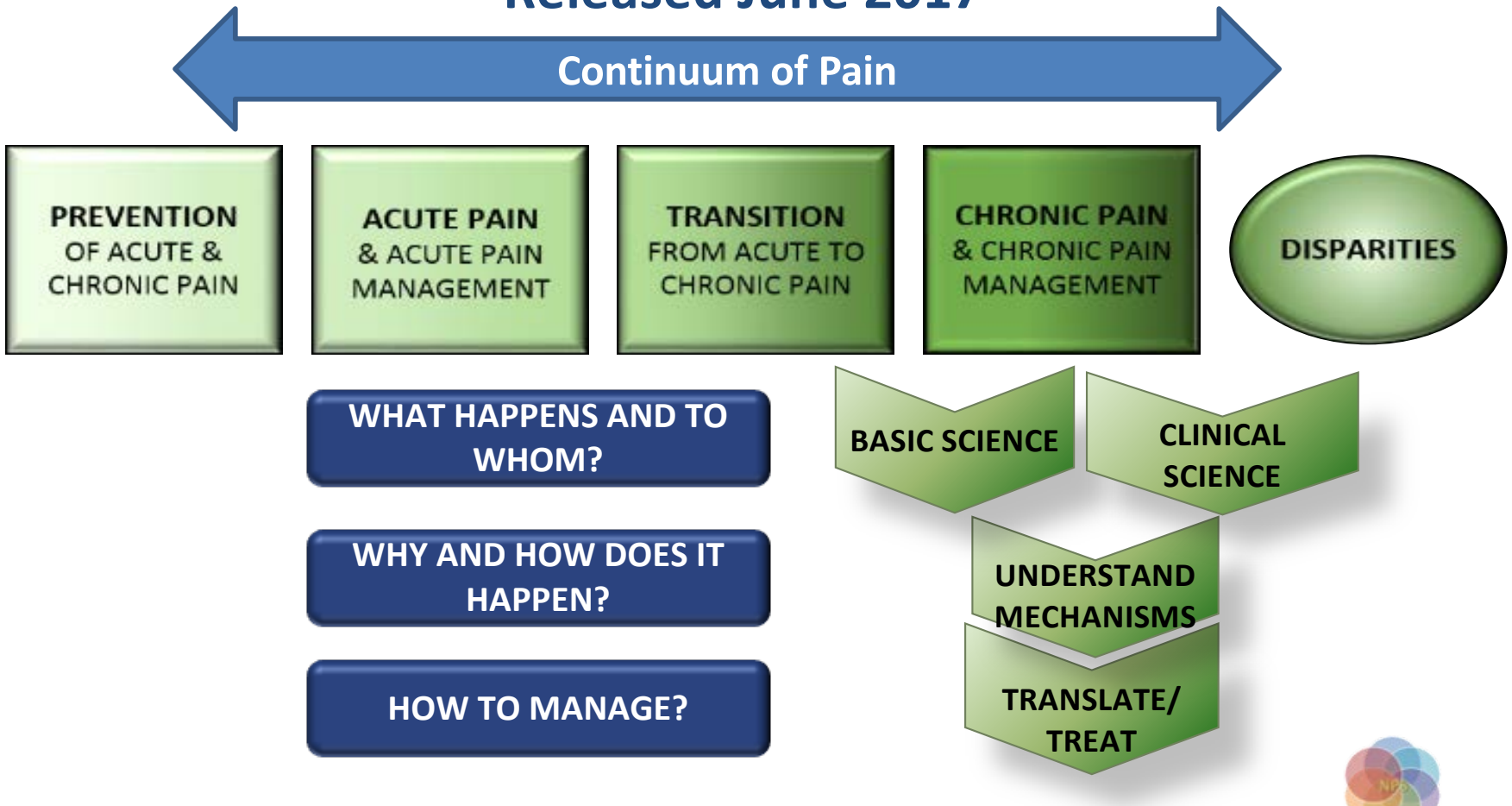
- population research;
- prevention and care;
- disparities;
- service delivery and payment;
- training and professional/public education

OASH is coordinating trans-agency implementation

National Pain Strategy

Federal Pain Research Strategy

Research Priorities to Guide the Federal Pain Research Agenda Released June 2017



NIH The Interagency Pain Research Coordinating Committee

NIH National Institute of Neurological Disorders and Stroke

https://iprcc.nih.gov/

NIH Pain Consortium
Centers of Excellence in Pain Education

CoEPEs
CENTERS OF EXCELLENCE IN PAIN EDUCATION

NIH funded Centers of Excellence in Pain Education were created to **develop, evaluate, and distribute pain management curriculum resources** (case based studies) for medical, nursing, dental, and pharmacy schools to enhance and improve how health care professionals are taught about pain and treatment of pain.

Peter, phantom limb pain


Morgan, 14, headaches


Edna, 70, chronic low back pain


Beverly, 46, burning mouth syndrome

Harvard University
University of Connecticut
University of Iowa
University of Washington
Johns Hopkins University
University of Rochester
Southern Illinois University
St. Louis University
University of Alabama at Birmingham
University of Pennsylvania
Pittsburgh University

https://painconsortium.nih.gov/NIH_Pain_Programs/CoEPES.html

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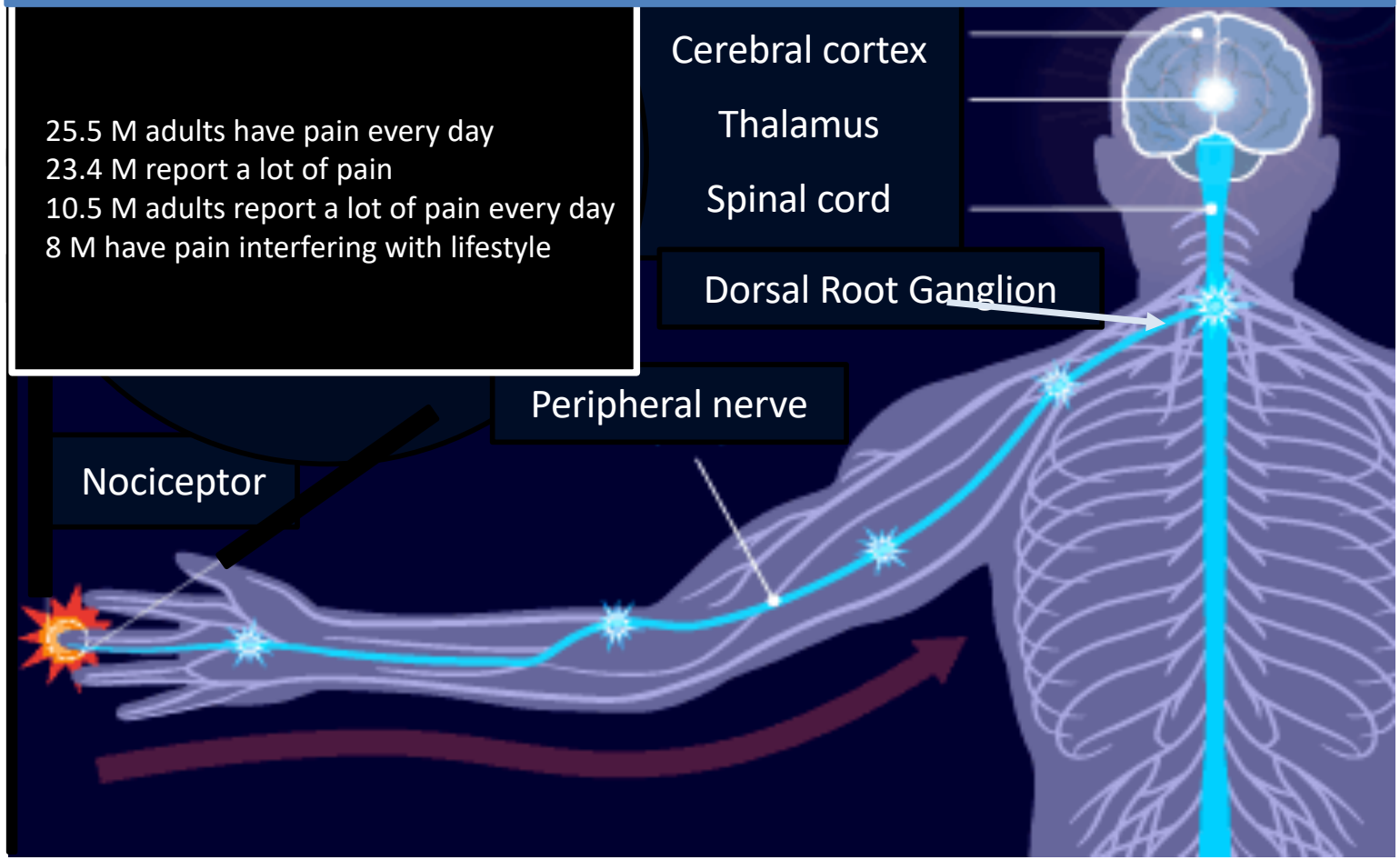
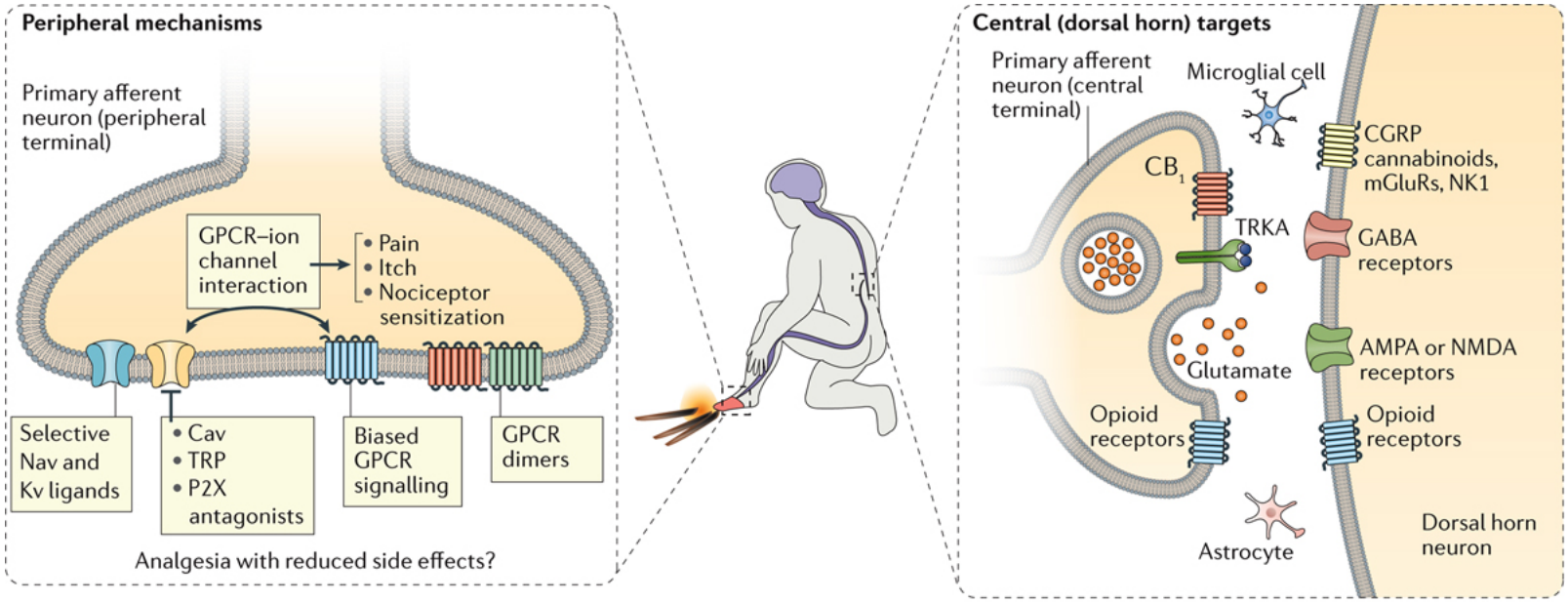
Opioids act on reward circuits as well as pain circuits. There are multiple non-opioid control nodes in the pain circuits that should be targeted for non addictive pain treatments.



Advances in pain research: New Targets for Pain

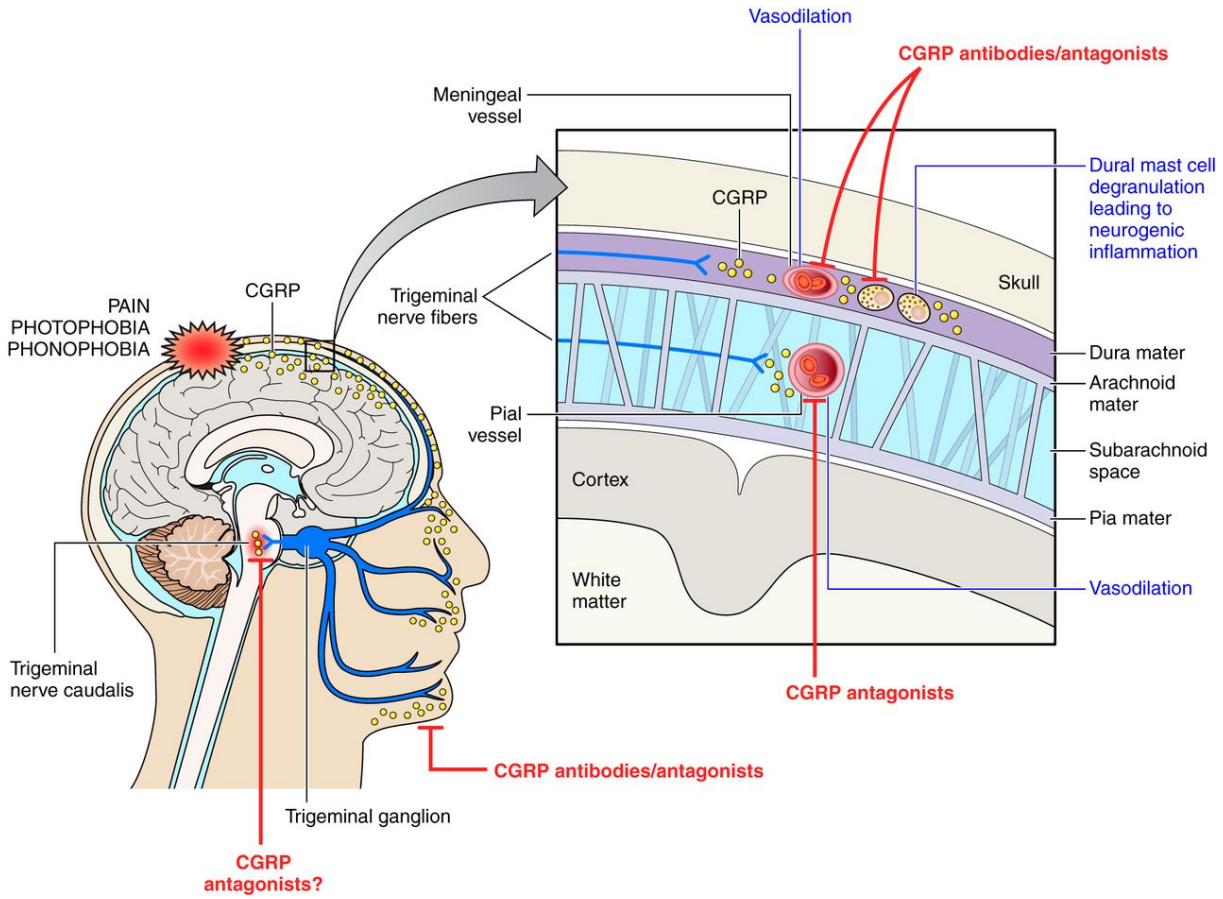


- HSV vector driven expression of analgesic signals in DRG
- Transient receptor potential channels (TRPA1/4)
  - TRPA1 gain of function mutation causes familial episodic pain syndrome
- Voltage activated Ca++ channel blockers
- K+ channels blockers
- Chemokine receptor antagonists
- Tetrahydropbiopterin from GTP release from injured neurons, polymorphisms in BCH1 enzyme linked to pain vulnerability
- Alpha2 adrenergic agonist
- Bivalent MOR with linked mGluR5 antagonist, CCR5 antagonist, delta OR antagonist,
- Epigenetic mechanisms involved in chronic pain
- microRNA cluster 183

Nat Rev Drug Discov. 2017 Aug;16(8):545-564

Advances in Pain Research: cGRP for Migraine

- Calcitonin gene-related peptide (cGRP) levels:
  - rise during spontaneous migraine attacks
  - Increased levels in serum in chronic migraine patients
  - decrease in response to triptans in parallel with symptomatic relief
- Kappa Opioid Receptor (KOR) antagonists block increased cGRP
- Anti-cGRP Monoclonal antibodies are in phase 3 clinical trials for migraine prevention



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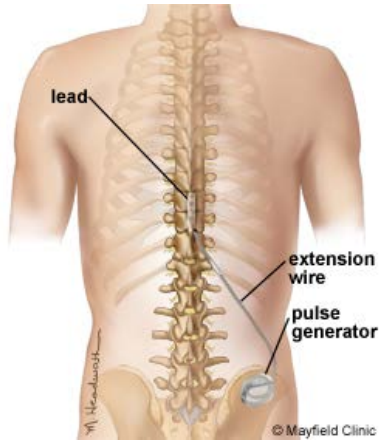
Curr Treat Options Neurol. 2017 Aug;19(8):27.
Cephalalgia. 2017 Jul;37(8):780-794.

Advances in pain research: Spinal Cord Stimulation and Opioid Use

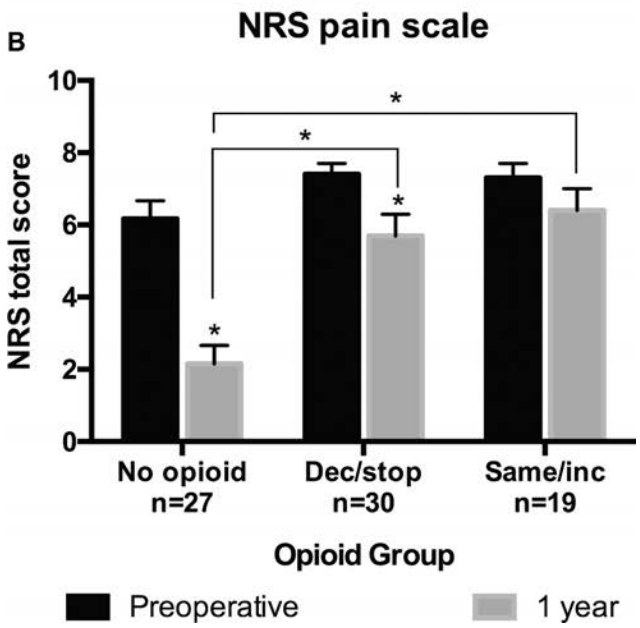
RESEARCH—HUMAN—CLINICAL STUDIES

Lucy Gee, PhD*
Heather C. Smith, MD‡
Zohal Ghulam-Jelani, BS*‡
Hirah Khan, BS‡
Julia Prusik, BS*‡
Paul J. Feustel, PhD*
Sarah E. McCallum, PhD*
Julie G. Pilitsis, MD, PhD*‡

Spinal Cord Stimulation for the Treatment of Chronic Pain Reduces Opioid Use and Results in Superior Clinical Outcomes When Used Without Opioids



- 86 patients underwent SCS for chronic pain
  - 53 had used opioids for pain prior to surgery
- 64% of patients who were using opioids prior to SCS reduced (n = 2) or eliminated opioid use (n = 29) at 1 yr postoperatively
- Patients who eliminated opioid use or never used opioids had superior clinical outcomes to those who continued use.



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Neurosurgery. 2018 Mar 12. doi: 10.1093/neuros/nyy065.

Advances in Pain Research: FDA Approval for Vagus Nerve Stimulation in Headache

Curr Pain Headache Rep. 2015 Dec;19(12):54.

gammaCore® Receives FDA Clearance for the Acute Treatment of Pain Associated with Migraine Headache in Adult Patients

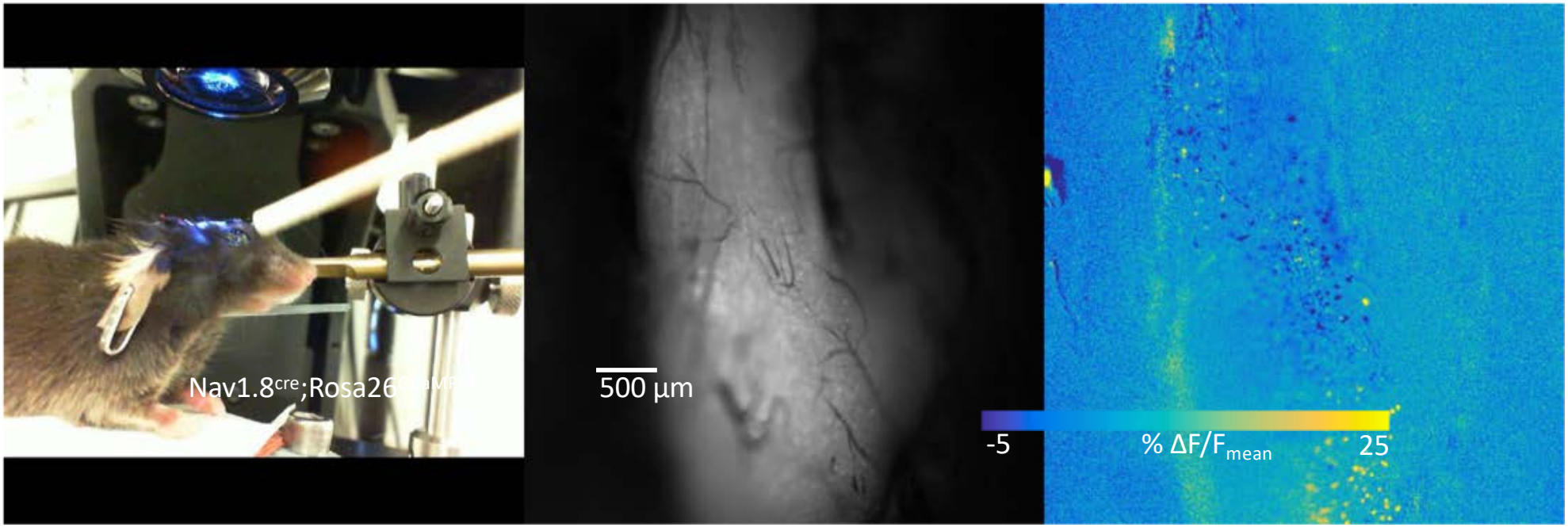
First non-invasive vagus nerve stimulation therapy applied at the neck provides new option for Americans living with migraine

electroCore

FDA Releases gammaCore®, the First Non-Invasive Vagus Nerve Stimulation Therapy Applied at the Neck for Acute Treatment of Pain Associated with Episodic Cluster Headache in Adult Patients

Tools from the NIH BRAIN Initiative enable precise monitoring and modulation of neural circuit activity

Live cell imaging of GCaMP responses
in Nav1.8+ trigeminal ganglion neurons



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NIH Support for Research in Multidisciplinary Pain Management Strategies

PI: Lynn DeBar, UH3NS088731

- Pragmatic clinical trial
- Hypothesis: patients who receive an interdisciplinary biopsychosocial intervention at their primary care clinic will have a greater reduction in pain impact in the year following than patients receiving usual care

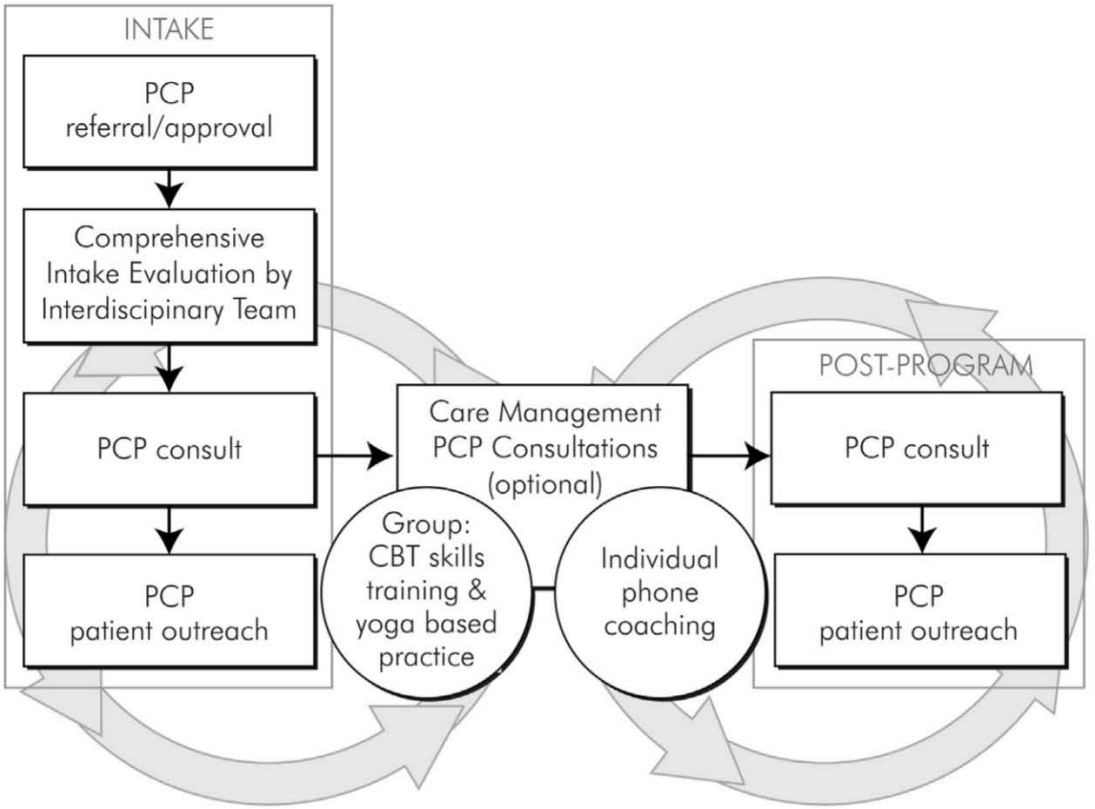

Fig. 2. PPACT intervention description.

Contemp Clin Trials. 2018 Apr;67:91-99.

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HEAL Initiative

Helping to End Addiction Long-term (HEAL) Initiative

1. **Prevent addiction through enhanced pain management**
   - Understand Origins of Chronic Pain
   - Develop New Non-Addictive Treatments for Pain
   - Build Clinical Trial Network for Chronic Pain
   - Enhance Precision Pain Management

2. **Improve treatments for opioid misuse disorder and addiction**
   - Improve Therapeutic Approaches to Addiction
   - Evaluate Treatments, Consequences of NOWS
   - Optimize Effective Treatments through Pilot Demonstration Projects

Announced April 4, 2018

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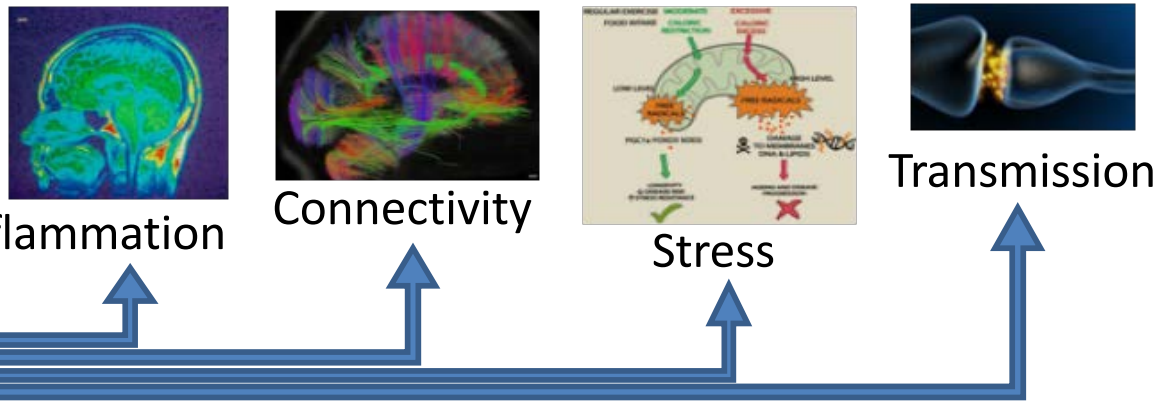
Biomarkers to Accelerate the Development of Non-Addictive Pain Medications



The goal is to <u>discover</u>, <u>optimize</u>, and <u>validate</u> objective mechanistic markers associated with pain conditions to:

1. Enrich clinical study population:
   - ✓ Allow or improve cohort stratification
   - ✓ Provide predictors of treatment response
2. Demonstrate therapeutic target engagement

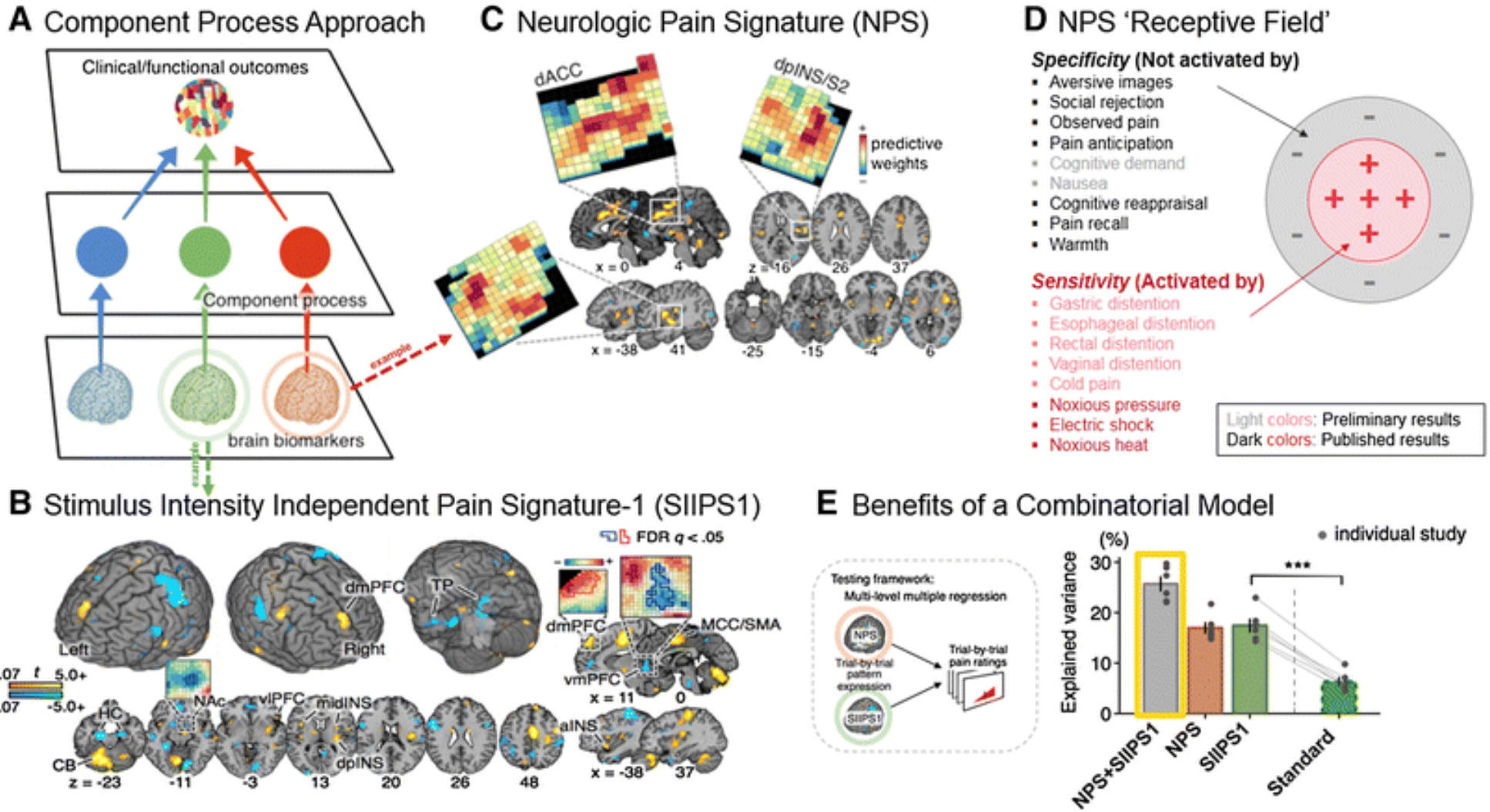
NINDS Pain Biomarker Efforts

- Workshop focused on "Best Practices for Biomarker Discovery" early 2019
- NINDS funding opportunities →
- Centralized NINDS "one-stop" biomarker web page

Analytical Validation of a Candidate Biomarker For Neurological Disease	Clinical Validation of a Candidate Biomarker For Neurological Disease
*PAR-NS-18-549, *PAR-18-550	*PAR-NS-18-548, *PAR-NS-18-664

Cooperative Agreement Grant Mechanisms: U01 (Academic) and U44 (SBIR)

fMRI as a Biomarker for Pain



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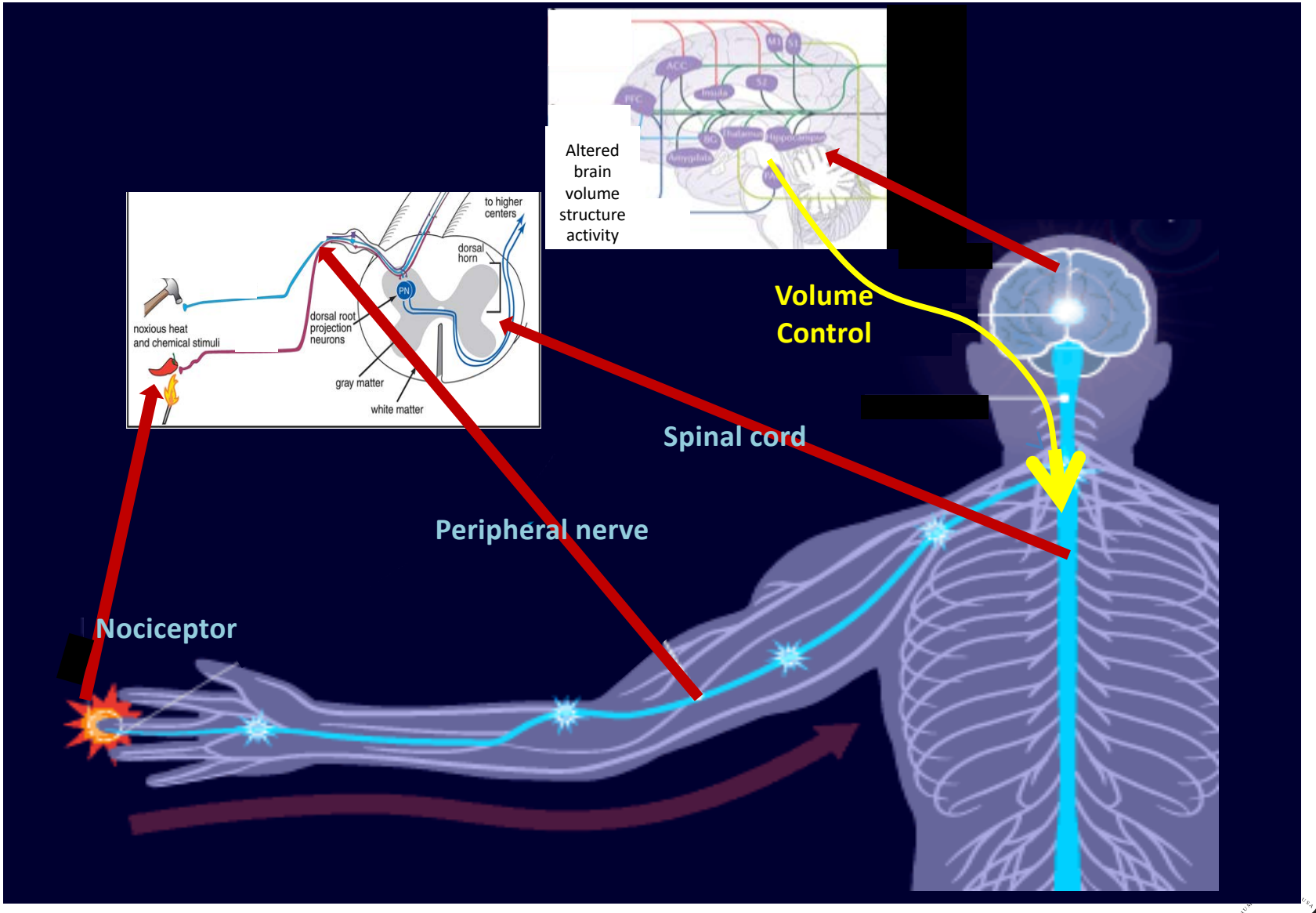
Neurosci Bull. 2018 Feb;34(1):208-215.

Neural Circuitry Changes with Chronic Pain



Common Fund: Can we prevent chronic pain?

Gap: Risk predictors of the transition from acute to chronic pain

Goal: Identify those at risk for transition to chronic pain through mechanistic objective signatures

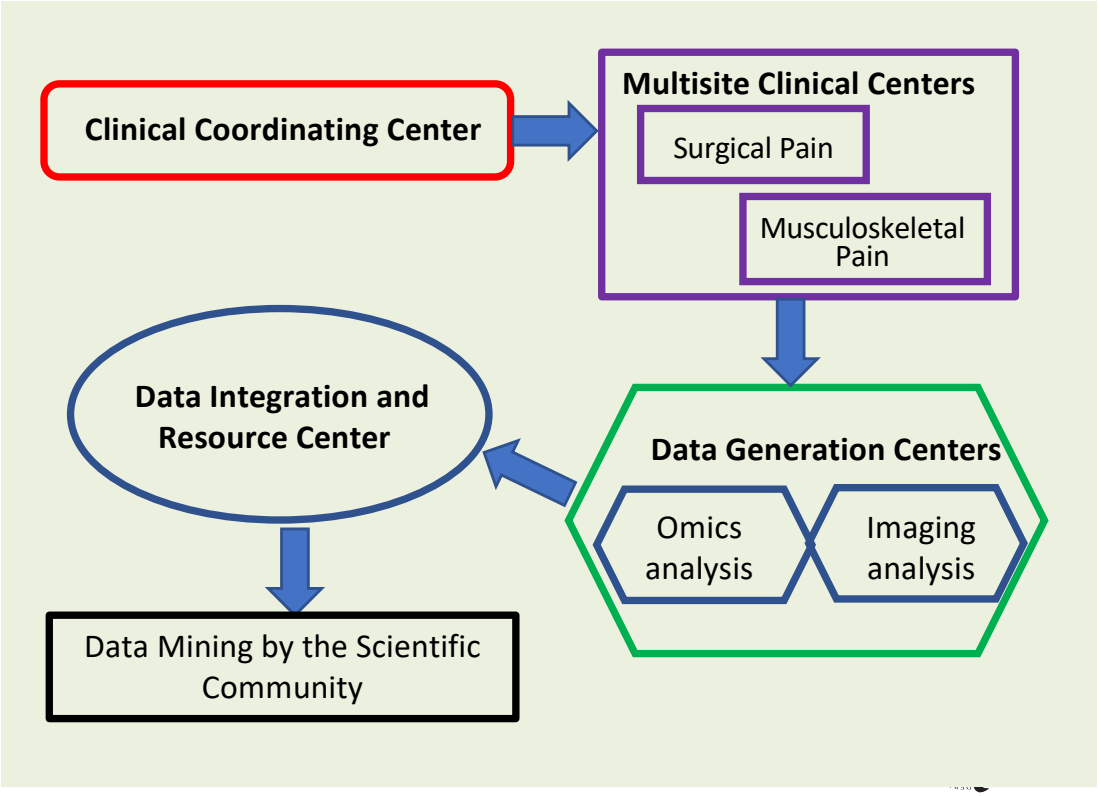
- Phenotyping, genotyping
- Imaging
- Omics

Justification

- Pain mechanisms
- Novel druggable targets
- Cohort stratification
- Prevention strategies

Outcomes

- Identification of combined biomarkers with clinically meaningful predictive value
- Comprehensive data set



Thank You!

Walter J. Koroshetz, M.D.

Director

National Institute of Neurological Disorders and Stroke

Email: koroshetzw@ninds.nih.gov

Website: http://www.ninds.nih.gov/

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